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## **Common mechanistic pathways in cancer and heart failure. A scientific roadmap on behalf of the Translational Research Committee of the Heart Failure Association (HFA) of the European Society of Cardiology (ESC)**

de Boer, Rudolf A ; Hulot, Jean-Sébastien ; Tocchetti, Carlo Gabriele ; et al ; Ruschitzka, Frank

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# Common mechanistic pathways in cancer and heart failure. A scientific roadmap on behalf of the Translational Research Committee of the Heart Failure Association (HFA) of the European Society of Cardiology (ESC)

**Rudolf A. de Boer<sup>1\*</sup>, Jean-Sébastien Hulot<sup>2,3</sup>, Carlo Gabriele Tocchetti<sup>4</sup>, Joseph Pierre Aboumsallem<sup>1</sup>, Pietro Ameri<sup>5,6</sup>, Stefan D. Anker<sup>7</sup>, Johann Bauersachs<sup>8</sup>, Edoardo Bertero<sup>9</sup>, Andrew J.S. Coats<sup>10</sup>, Jelena Čelutkienė<sup>11</sup>, Ovidiu Chioncel<sup>12</sup>, Pierre Dodion<sup>13</sup>, Thomas Eschenhagen<sup>14,15</sup>, Dimitrios Farmakis<sup>16,17</sup>, Antoni Bayes-Genis<sup>18,19,20</sup>, Dirk Jäger<sup>21</sup>, Ewa A. Jankowska<sup>22</sup>, Richard N. Kitsis<sup>23</sup>, Suma H. Konety<sup>24</sup>, James Larkin<sup>25</sup>, Lorenz Lehmann<sup>26,27,28</sup>, Daniel J. Lenihan<sup>29</sup>, Christoph Maack<sup>9</sup>, Javid J. Moslehi<sup>30</sup>, Oliver J. Müller<sup>31,32</sup>, Patrycja Nowak-Sliwinska<sup>33,34</sup>, Massimo Francesco Piepoli<sup>35</sup>, Piotr Ponikowski<sup>22</sup>, Radek Pudil<sup>36</sup>, Peter P. Rainer<sup>37</sup>, Frank Ruschitzka<sup>38</sup>, Douglas Sawyer<sup>39</sup>, Petar M. Seferovic<sup>40</sup>, Thomas Suter<sup>41</sup>, Thomas Thum<sup>42</sup>, Peter van der Meer<sup>1</sup>, Linda W. Van Laake<sup>43</sup>, Stephan von Haehling<sup>44,45</sup>, Stephane Heymans<sup>46,47</sup>, Alexander R. Lyon<sup>48</sup>, and Johannes Backs<sup>49,50</sup>**

<sup>1</sup>Department of Cardiology, University Medical Center Groningen, Groningen, The Netherlands; <sup>2</sup>Université de Paris, PARCC, INSERM, Paris, France; <sup>3</sup>CIC1418 and DMU CARTE, AP-HP, Hôpital Européen Georges-Pompidou, Paris, France; <sup>4</sup>Department of Translational Medical Sciences and Interdepartmental Center of Clinical and Translational Research, Federico II University, Naples, Italy; <sup>5</sup>Department of Internal Medicine and Center of Excellence for Biomedical Research, University of Genova, Genoa, Italy; <sup>6</sup>Cardiovascular Disease Unit, IRCCS Ospedale Policlinico San Martino, Genoa, Italy; <sup>7</sup>Department of Cardiology & Berlin Institute of Health Center for Regenerative Therapies (BCRT), German Center for Cardiovascular Research (DZHK), Partner Site Berlin, Charité-Universitätsmedizin Berlin (Campus CVK), Berlin, Germany; <sup>8</sup>Department of Cardiology and Angiology, Hannover Medical School, Hannover, Germany; <sup>9</sup>Comprehensive Heart Failure Center, University Clinic Würzburg, Würzburg, Germany; <sup>10</sup>San Raffaele Pisana Scientific Institute, Rome, Italy; <sup>11</sup>Clinic of Cardiac and Vascular Diseases, Institute of Clinical Medicine, Faculty of Medicine, Vilnius University, Vilnius, Lithuania; <sup>12</sup>Emergency Institute for Cardiovascular Diseases 'Prof. C.C. Iliescu', University of Medicine Carol Davila, Bucharest, Romania; <sup>13</sup>Innate Pharma, Marseille, France; <sup>14</sup>Institute of Experimental Pharmacology and Toxicology, University Medical Center Hamburg-Eppendorf, Hamburg, Germany; <sup>15</sup>Partner Site Hamburg/Kiel/Lübeck, DZHK (German Centre for Cardiovascular Research), Hamburg, Germany; <sup>16</sup>University of Cyprus Medical School, Nicosia, Cyprus; <sup>17</sup>Cardio-Oncology Clinic, Heart Failure Unit, Department of Cardiology, Athens University Hospital 'Attikon', National and Kapodistrian University of Athens Medical School, Athens, Greece; <sup>18</sup>Heart Failure Unit and Cardiology Department, Hospital Universitari Germans Trias i Pujol, CIBERCV, Badalona, Spain; <sup>19</sup>Department of Medicine, Universitat Autònoma de Barcelona, Barcelona, Spain; <sup>20</sup>CIBER Cardiovascular, Instituto de Salud Carlos III, Madrid, Spain; <sup>21</sup>Department of Medical Oncology, National Center for Tumor Diseases (NCT), University Hospital Heidelberg, Heidelberg, Germany; <sup>22</sup>Department of Heart Diseases, Wrocław Medical University, and Centre for Heart Diseases, University Hospital, Wrocław, Poland; <sup>23</sup>Departments of Medicine (Cardiology) and Cell Biology, Wilf Family Cardiovascular Research Institute, Albert Einstein Cancer Center, Albert Einstein College of Medicine, New York, NY, USA; <sup>24</sup>Cardiovascular Division, Cardio-Oncology Program, Department of Medicine, University of Minnesota Medical School, Minneapolis, MN, USA; <sup>25</sup>Royal Marsden NHS Foundation Trust, London, UK; <sup>26</sup>Cardio-Oncology Unit, Department of Cardiology, University of Heidelberg, Heidelberg, Germany; <sup>27</sup>DZHK (German Centre for Cardiovascular Research), partner site, Heidelberg/Mannheim, Germany; <sup>28</sup>DKFZ (German Cancer Research Center), Heidelberg, Germany; <sup>29</sup>Cardio-Oncology Center of Excellence, Cardiovascular Division, Washington University in St. Louis, St. Louis, MO, USA; <sup>30</sup>Division of Cardiovascular Medicine and Oncology, Cardio-Oncology Program, Vanderbilt University Medical Center and Vanderbilt-Ingram Cancer Center, Nashville, TN, USA; <sup>31</sup>Department of Internal Medicine III, University of Kiel, Kiel, Germany; <sup>32</sup>DZHK (German Centre for Cardiovascular Research), partner site, Hamburg/Kiel/Lübeck, Germany; <sup>33</sup>School of Pharmaceutical Sciences, University of Geneva, Institute of Pharmaceutical Sciences of Western Switzerland, University of Geneva, Geneva, Switzerland; <sup>34</sup>Translational Research Center in Oncohaematology, Geneva, Switzerland;

\*Corresponding author: Department of Cardiology, University of Groningen, University Medical Center Groningen, PO Box 30.001, 9700 RB Groningen, The Netherlands. Tel: + 31 50 361 2355, Email: ra.de.boer@umcg.nl

<sup>35</sup>Heart Failure Unit, Cardiology, G. da Saliceto Hospital, Piacenza, University of Parma, Parma, Italy; <sup>36</sup>1st Department Medicine-Cardioangiopathy, University Hospital and Medical Faculty, Hradec Kralove, Czech Republic; <sup>37</sup>Medical University of Graz, University Heart Center – Division of Cardiology, Graz, Austria; <sup>38</sup>Department of Cardiology, University Hospital Zurich, University Heart Center, Zurich, Switzerland; <sup>39</sup>Center for Molecular Medicine, Maine Medical Center Research Institute, Maine Medical Center, Scarborough, ME, USA; <sup>40</sup>University of Belgrade Faculty of Medicine, Serbian Academy of Sciences and Arts, Belgrade, Serbia; <sup>41</sup>Swiss Cardiovascular Centre, Bern University, Bern, Switzerland; <sup>42</sup>Institute of Molecular and Translational Therapeutic Strategies (IMTTS), Hannover Medical School, Hannover, Germany; <sup>43</sup>Division Heart and Lungs and Regenerative Medicine Centre, University Medical Centre Utrecht and Utrecht University, Utrecht, The Netherlands; <sup>44</sup>Department of Cardiology and Pneumology, Heart Center, University of Göttingen Medical Center, Göttingen, Germany; <sup>45</sup>German Center for Cardiovascular Research (DZHK), partner site Göttingen, Göttingen, Germany; <sup>46</sup>Department of Cardiology, CARIM School for Cardiovascular Diseases Faculty of Health, Medicine and Life Sciences, Maastricht University, Maastricht, The Netherlands; <sup>47</sup>Department of Cardiovascular Sciences, Centre for Molecular and Vascular Biology, KU Leuven, Leuven, Belgium; <sup>48</sup>Cardio-Oncology Service, Royal Brompton Hospital, and National Heart and Lung Institute, Imperial College London, London, UK; <sup>49</sup>Institute of Experimental Cardiology, Heidelberg University Hospital, Heidelberg, Germany; and <sup>50</sup>DZHK (German Centre for Cardiovascular Research), partner site, Heidelberg/Mannheim, Germany

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The co-occurrence of cancer and heart failure (HF) represents a significant clinical drawback as each disease interferes with the treatment of the other. In addition to shared risk factors, a growing body of experimental and clinical evidence reveals numerous commonalities in the biology underlying both pathologies. Inflammation emerges as a common hallmark for both diseases as it contributes to the initiation and progression of both HF and cancer. Under stress, malignant and cardiac cells change their metabolic preferences to survive, which makes these metabolic derangements a great basis to develop intersection strategies and therapies to combat both diseases. Furthermore, genetic predisposition and clonal haematopoiesis are common drivers for both conditions and they hold great clinical relevance in the context of personalized medicine. Additionally, altered angiogenesis is a common hallmark for failing hearts and tumours and represents a promising substrate to target in both diseases. Cardiac cells and malignant cells interact with their surrounding environment called stroma. This interaction mediates the progression of the two pathologies and understanding the structure and function of each stromal component may pave the way for innovative therapeutic strategies and improved outcomes in patients. The interdisciplinary collaboration between cardiologists and oncologists is essential to establish unified guidelines. To this aim, pre-clinical models that mimic the human situation, where both pathologies coexist, are needed to understand all the aspects of the bidirectional relationship between cancer and HF. Finally, adequately powered clinical studies, including patients from all ages, and men and women, with proper adjudication of both cancer and cardiovascular endpoints, are essential to accurately study these two pathologies at the same time.

## Keywords

Heart failure • Cancer • Cardiotoxicity • Inflammation • Clonal haematopoiesis • Angiogenesis • Metabolism • Cardio-oncology • Extracellular matrix

## Introduction

Advances in pharmacological and device therapies of heart failure (HF), along with a holistic approach provided by multidisciplinary HF teams, have improved management and reduced cardiovascular (CV) death and sudden cardiac death in particular.<sup>1–3</sup> However, this has led to a relative shift towards a chronic state of HF with an increasing burden of comorbidities. Most attention has been focused on atherosclerosis, renal disease, diabetes mellitus, and atrial fibrillation as common comorbidities in chronic HF. However, relatively little awareness has been given to cancer, which nevertheless appears to be a common disease and the leading cause of non-CV mortality in chronic HF.<sup>2–5</sup>

On the other hand, recent improvements in cancer management and treatments have substantially reduced mortality associated with many cancer types, while concomitantly increasing the comorbidity burden of oncological patients. CV disease is the most frequent non-cancer cause of death in patients with cancer, and an increased risk of incident HF has been reported amongst patients diagnosed with cancer. This is largely attributed to the cardiotoxicity of anti-cancer agents and/or radiation therapy.<sup>6,7</sup>

Cancer and HF share several common risk factors. Beyond this, the two entities share common systemic pathogenic pathways and

mechanisms that partly explain their association.<sup>8</sup> Consequently, the connection between CV disease and cancer emerged as a new discipline that encourages collaborations between oncologists and cardiologists at clinical and research levels, and thereby aims to optimize the management of individuals affected by these pathologies. The inclusion of both specialties in the design of future pre-clinical and clinical studies should ensure precise, reproducible, and meaningful readouts for both cancer and HF.

The present document, derived by an expert panel meeting organized by the Translational Research Committee of the Heart Failure Association of the European Society of Cardiology, aims to highlight the common pathways potentially underlying both HF and cancer. Moreover, this manuscript summarizes available evidence and provides guidance to bridge past and future research approaches.

## Coexistence of cancer and heart failure

A large number of epidemiological studies suggest that the incidence of several malignant tumours is higher in patients with HF compared to age- and sex-matched controls. A community-based cohort study reported that HF patients carried a 68% higher risk

**Table 1** Common imaging, laboratory tests or drugs that may reveal or unmask cancer in heart failure patients

Test/drugs	Indication/reason	Form of cancer that may be detected
Chest X-ray	Dyspnoea	Lung cancer
	Control for ICD leads	Lymphoma
Chest CT scan	Suspicion for PE	Lung cancer
	Pre-ablation (LA appendage, anatomy of pulmonary veins)	Lymphoma
	Anatomy of aorta	Oesophageal cancer
		Gastric cancer
		Liver cancer and metastases
Cardiac MRI	Cardiomyopathies	Lung cancer
	Congenital heart disease	Lymphoma
		Oesophageal cancer
		Gastric cancer
		Liver cancer and metastases
		AL amyloidosis
PET scan	Endocarditis (valvular, PM/ICD, PM/ICD leads)	All forms of cancer
Lab tests	Haemoglobin, MCV, iron, TSAT	Gastrointestinal cancers
		Genitourinary cancers
		Lymphoma, leukaemia
	Liver tests	Liver cancer
		Hepatic metastases of other cancers
	BSR CRP	Lymphoma, leukaemia
Use of antithrombotic drugs	CAD, AF, prosthetic material (valves)	Gastrointestinal cancers
		Genitourinary cancers

AF, atrial fibrillation; BSR, blood sedimentation rate; CAD, coronary artery disease; CRP, C-reactive protein; CT, computed tomography; ICD, implantable cardioverter-defibrillator; LA, left atrium; MCV, mean corpuscular volume; MRI, magnetic resonance imaging; PE, pulmonary embolism; PET, positron emission tomography; PM, pacemaker; TSAT, transferrin saturation.

of incident malignancy compared to the general population,<sup>9</sup> and incident cancer in HF was associated with a 56% excess adjusted mortality risk. In a subsequent study, the same investigators retrospectively evaluated 1081 first myocardial infarction (MI) survivors and observed that patients who developed HF within 30 days of MI had a 71% higher incidence of cancer compared to those without HF.<sup>10</sup> These observations were confirmed by a Danish HF cohort study reporting a higher risk of cancer over a 4.5-year follow-up period in patients with HF, also even after excluding all cancers that occurred within a year of HF diagnosis.<sup>11</sup> There are conflicting results however: in the Physicians' Health Study, (self-reported) HF was not associated with an increased cancer incidence nor cancer-specific mortality in 28 341 males enrolled.<sup>12</sup> But overall, data from a large longitudinal HF registry indicate a remarkable increase in the incidence of cancer deaths among HF patients over the last decades, and<sup>2</sup> several cancer types are consistently reported to develop in HF patients, such as lung cancer, skin cancer, haematological malignancies, and colorectal cancer.<sup>8</sup>

Table 1 summarizes common tests and drugs that may potentially uncover cancer in HF patient. HF patients are typically under closer medical observation than the non-HF populations. Repeated radiological examinations [chest X rays and computed tomography (CT) scans], as well as cardiac positron emission tomography (PET) scans, and magnetic resonance imaging (MRI) scans, frequently detect incidental tumours. HF patients also undergo frequent blood tests, including markers of iron metabolism and haematinics,

which may trigger workup for suspected cancer. Consequently, cancer will be detected at early stages due to surveillance. Second, a large proportion of HF patients are treated with oral anticoagulant drugs or antiplatelet therapies, which are known to cause bleeding and unmask gastrointestinal and genitourinary cancers, and this may prompt early detection.<sup>13</sup>

Discrepancies among the outcomes of numerous cohorts are a clear drawback, and high-quality data are urgently required. The apparent inconsistencies are explained by differences in cancer and HF diagnoses, guidelines, and strategies. Another reason could be the small sample sizes,<sup>9,10</sup> short follow-up period,<sup>9–11</sup> lack of adjustment for smoking status and HF severity,<sup>11</sup> availability of only self-reported data, poor cancer adjudication in HF databases, or limited data obtained in women.<sup>12</sup> It should be pointed out that most evidence originates from associations identified in retrospective analyses. This has inherent limitations in that causality is not guaranteed and that retrospective analyses are hampered by their original design, generally under powered toward specific cancer outcomes.

## Common mechanisms involved in tumour growth and heart failure

The association between HF and cancer is partly explained by common risk factors.<sup>14–17</sup> Nevertheless, even when adjusting for

these risk factors, the incidence of new-onset cancer in prevalent CV disease and HF is not fully explained. A growing body of experimental and clinical evidence is unveiling several mechanisms potentially underlying both HF and cancer. Inflammation, metabolic remodelling, clonal haematopoiesis, angiogenesis, as well as the extracellular matrix (ECM) and stromal cells are of interest in this regard.<sup>18</sup>

## Inflammation

Circulating levels of pro-inflammatory cytokines, including, interleukin (IL)-1 $\beta$ , IL-6 and IL-18, are elevated in chronic as well as acute decompensated HF.<sup>19</sup> Solid malignancies exhibit several features that are typical of inflamed tissues, such as the infiltration of immune cells and the production of pro-inflammatory mediators, and numerous studies emphasize the key role of inflammation as a mediator of malignant transformation, epithelial to mesenchymal transition, and metastasis.<sup>20,21</sup> Further, IL-1 $\beta$  and IL-6 have been reported as important drivers of cancer.<sup>22–25</sup>

Lending support to this hypothesis, the Canakinumab Anti-Inflammatory Thrombosis Outcome Study (CANTOS) demonstrated a favourable impact of the IL-1 $\beta$ -targeting antibody canakinumab on CV events and HF hospitalization. Strikingly, this study suggests the possibility that canakinumab could significantly decrease incident lung cancer and lung cancer mortality. Nevertheless, the overall rate of cancer was 1.8 per 100 patient-years and not significantly different among study intervention arms. Thus, these results should be interpreted carefully and the replication of these outcomes is required.<sup>26,27</sup>

In addition to cytokines and chemokines, lipid mediators such as prostanoids are involved in inflammatory signalling, but their role in cancer and CV disease has not been extensively investigated so far. For instance, prostaglandin E<sub>2</sub> levels are elevated in cancer, especially in gastrointestinal tumours, and this prostanoid promotes cancer initiation and suppresses the immune response directed against cancer cells.<sup>28,29</sup> Prostaglandin E<sub>2</sub> can also affect cardiac function by activating maladaptive gene programs downstream of the EP3 receptor on cardiomyocytes, and cardiomyocytes in turn secrete chemokines and can induce chemoattractant signalling.<sup>30,31</sup> Prostacyclin and prostaglandin analogues are used to treat pulmonary arterial hypertension. A pre-clinical study showed that prostaglandin E<sub>2</sub> promotes lung cancer migration.<sup>32</sup> Another study in mice revealed that prostacyclin prevents lung cancer.<sup>33</sup> However, cancer incidence has not been assessed in patients with pulmonary hypertension treated with prostaglandins or analogues.

Recent reviews have extensively discussed inflammation as a potential link between cancer and HF, which encourages further research to provide deeper insights on this topic.

## Metabolic remodelling as a common hallmark for cancer and heart failure

Malignant and cardiac cells undergo metabolic reprogramming to adapt to physiological transformations, survive, and respond

to stress. In tumours and failing hearts, glucose oxidation and glycolysis are required to ensure ATP provision and to produce metabolic intermediates that are essential for the synthesis of macromolecules, such as fatty acids and nucleotides. Specifically, cancer cells tend to be predominantly reliant on glucose metabolism, but in contrast to differentiated cells they convert glucose into lactate also in the presence of oxygen levels sufficient to sustain oxidative metabolism, the so-called 'Warburg effect'.<sup>34</sup> This overreliance on this aerobic glycolysis facilitates the incorporation of nutrients into nucleotides, amino acids, and lipids that are required to sustain cancer cell proliferation.<sup>35</sup> In addition to glucose, the amino acid glutamine represents an essential carbon source to support the use of Krebs cycle and glucose-derived intermediates as precursors for the biosynthesis of macromolecules in cancer cells.<sup>36</sup>

The healthy myocardium predominantly uses fatty acids to sustain ATP synthesis,<sup>37,38</sup> but substrate preference and metabolic flexibility of the heart are altered under pathological conditions.<sup>39</sup> For instance, the switch from fatty acids to glucose during pressure overload remodels metabolic fluxes to support biomass synthesis, thereby contributing to the hypertrophic growth of the heart, and protein O-GlcNAcylation, thereby contributing to calcium mishandling and cardiac dysfunction.<sup>40–43</sup> Thus, metabolic reprogramming in both cancer cells and cardiomyocytes is directed toward the synthesis of anabolic precursors that are required to support cell proliferation and hypertrophy, respectively. However, important differences in metabolic reprogramming exist between tumours and the heart; for instance, in contrast to cancer cells, cardiomyocytes do not rely on glutamine for aspartate synthesis.<sup>40,44</sup>

In the context of cancer, several therapeutic strategies target pathways that mediate energy homeostasis and macromolecule biosynthesis. As an example, the inhibition of glucose transporter 1 (GLUT1), *in vitro* and *in vivo*, diminished tumour growth.<sup>45</sup> Conversely, cardiac-specific overexpression of GLUT1 in transgenic mice demonstrated preventive capacities against cardiac hypertrophy.<sup>46</sup> Further, sodium–glucose co-transporter 2 (SGLT2) inhibition, which is an effective treatment for type 2 diabetes, exhibits beneficial effects particularly in HF. In addition, preliminary evidence from animal studies suggests a potential future role of SGLT2 inhibition for the treatment of particular cancer types.<sup>47</sup> However, more extensive research is required before definitive conclusions can be drawn regarding this clinical application.

Other therapeutics targeting lipid metabolism have been explored. For instance, fatty acid synthase (FAS), which is a key enzyme of *de novo* lipogenesis, is up-regulated in many malignancies. Pre-clinical and clinical studies revealed that FAS inhibitors demonstrated anti-neoplastic properties in solid cancers.<sup>48</sup> In the context of HF, FAS was increased in 2 mouse models of HF and human hearts with end-stage cardiomyopathy.<sup>49</sup> Consequently, FAS represents a potential therapeutic target for both conditions.

The common metabolic derangements between cancer and HF provide opportunities to develop intersection strategies and therapies to combat both diseases.



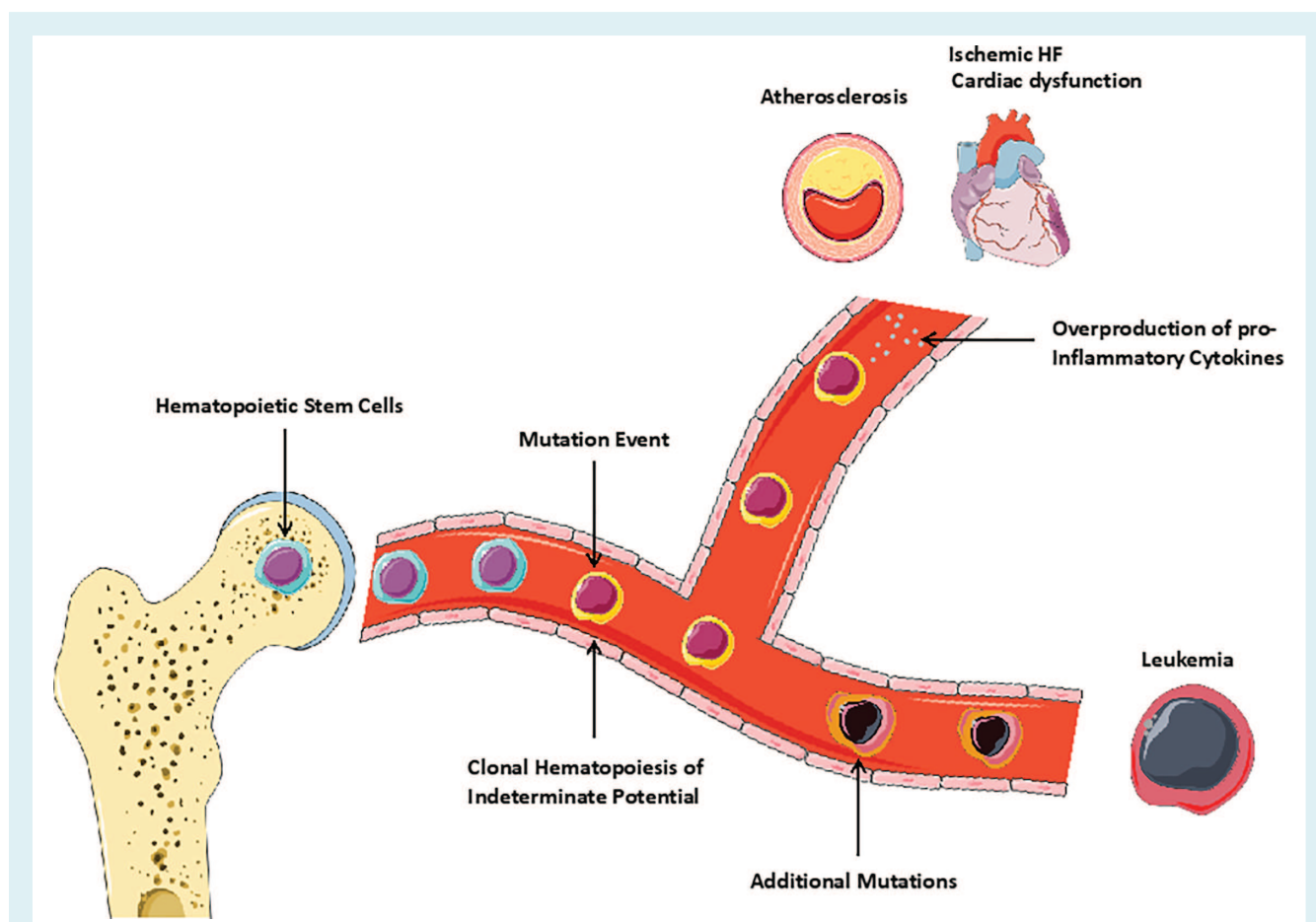
## Clonal haematopoiesis of indeterminate potential

Genetic risk factors are also emerging as potential common drivers of cancer and CV disease (Figure 1).<sup>50</sup> Ground-breaking studies indicate that acquired somatic mutations in haematopoietic cells are associated with a markedly increased risk of coronary heart disease in humans.<sup>51</sup> The majority (>70%) of these mutations occur in Ten-eleven translocation-2 (*TET2*), DNA methyltransferase 3 alpha (*DNMT3α*), additional sex combs like 1 (*ASXL1*), Janus kinase 2 (*JAK2*), and tumour protein 53 (*TP53*),<sup>51,52</sup> that encode for key epigenetic regulators of haematopoiesis and whose mutation confers a competitive growth advantage leading to the progressive clonal expansion of the mutated lineage. Clonal haematopoiesis can progress to leukaemia<sup>53</sup> but portends an increased risk of CV disease and stroke independent of whether it becomes clinically overt.<sup>51,54</sup> Furthermore, somatic mutations in *TET2* and *DNMT3α* are associated with worse outcomes in patients with ischaemic HF.<sup>55</sup> Whether and how clonal haematopoiesis promotes atherosclerosis is not completely

understood, but pre-clinical studies reported that the expression of pro-inflammatory cytokines by *TET2*-deficient macrophages is exacerbated in atherosclerosis-prone mice, consequently accelerating plaque formation.<sup>51,56</sup> In two murine models of HF, haematopoietic *TET2* or *DNMT3α* deficiency aggravated cardiac dysfunction, which was rescued by pharmacological inhibition of the Nod-like receptor protein 3 (NLRP3) inflammasome.<sup>57,58</sup> Elucidating the mechanisms linking somatic mutation-driven clonal haematopoiesis to CV disease holds great clinical promise in the context of personalized medicine, as it will provide insight into the predictive value of these mutations as markers of CV risk and therapeutic responsiveness.

## Angiogenesis

Angiogenesis is the process of new blood vessel formation from existing vessels and is crucially involved in the pathophysiology of both HF and malignancies. During the early stage of chronic pressure overload, cardiomyocyte hypertrophy leads to a mismatch between capillary density and increased oxygen demand.



**Figure 1** Graphic illustration showing somatic mutations in haematopoietic stem cells as a common path for cancer (leukaemia) and cardiovascular disease.<sup>50</sup> In individuals with a single somatic mutation, the development of leukaemia requires additional mutations. These individuals are exposed to a higher risk of developing heart failure (HF) and atherosclerosis. This may be due to the overproduction of pro-inflammatory cytokines by cells with somatic mutations. Illustration elements are from Smart Servier Medical Art.

The consequent hypoxia stimulates microvascular expansion by inducing secretion of angiogenic factors, such as vascular endothelial growth factor (VEGF) and angiopoietin-1 and -2.<sup>59</sup> With sustained pressure overload, however, this adaptive angiogenic response is suppressed, and the subsequent vascular rarefaction contributes to the transition to decompensated HF.<sup>60,61</sup> The pharmacological or genetic inhibition of VEGF, as well as the blockade of other key angiogenic signalling pathways, accelerate the transition to HF.<sup>59,60,62,63</sup>

In the context of cancer, angiogenesis is crucial for tumour growth and dissemination.<sup>64</sup> New blood vessel formation is required to nourish cancer cells when tumour growth prevents the diffusion of nutrients from the pre-existing vasculature. Furthermore, malignant neoplasms take advantage of the dysfunctional tumour vessels to spread throughout the body.<sup>64</sup> Drugs inhibiting angiogenesis, such as VEGF inhibitors, have been employed in the treatment of several types of malignancies, including colorectal, kidney, brain, and lung cancer. The CV toxicities of these agents are potentially severe, and often unpredictable. Based on these findings, angiogenesis represents a favourable substrate for both diseases.

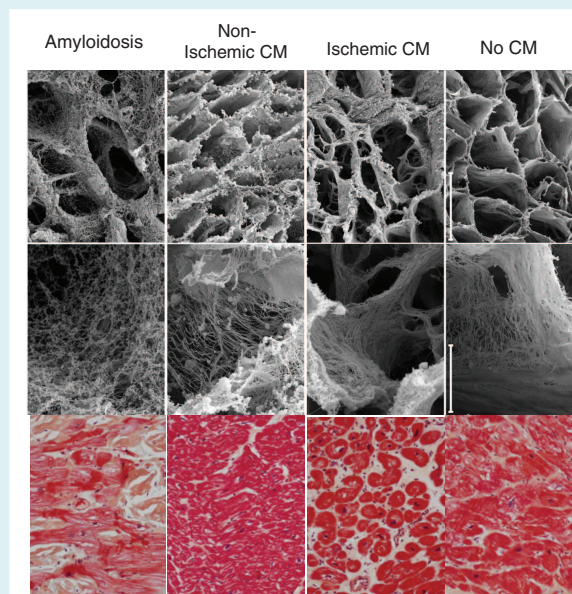
## Stromal cells and extracellular environment

In tumours, malignant cells coexist with the ECM and other cell types that constitute the so-called tumour stroma. The paracrine interactions between neoplastic cells and stromal cells, and among stromal cells, promote tumour growth, progression, and invasiveness.<sup>65</sup> Besides cardiomyocytes, the heart contains diverse cardiac stromal cell lineages that play key roles in heart repair, regeneration, and disease.<sup>66</sup>

Cardiomyopathy and HF in cancer patients do not only result from an intrinsic injury.<sup>67</sup> Figure 2 presents the diffuse effects on the ECM in the heart either from intrinsic injury via cardiotoxicity related to chemotherapy, or extrinsic to the heart as evidenced by proteotoxicity seen with AL amyloidosis. Similarly, the ECM in tumours mediates cancer progression and development and plays a crucial role in anti-cancer treatment resistance.<sup>68,69</sup>

The intramyocardial transplantation of FAC-purified human microvascular pericytes promotes functional and structural recovery post-infarction via paracrine effects and cellular interactions. These therapeutic pericytes activate cardio-protective mechanisms that reverse ventricular remodelling, decrease cardiac fibrosis, reduce chronic inflammation, and promote angiogenesis.<sup>70</sup> In the context of cancer, blocking pericytes has failed to improve outcome in cancer patients. In fact, targeting pericytes could increase metastasis under certain circumstances.<sup>71</sup>

In HF, quiescent fibroblasts are replaced by proliferative fibroblasts that alter the myocardial matrix and convert it to a fibrotic structure, which makes the myocardium stiffer. In solid tumours, fibroblasts act similarly and promote structural changes in the surrounding stroma to allow tumour growth and invasion. In both conditions, abnormal fibroblasts are characterized by the co-localization of extra proteins that are associated with various biological functions. Fibroblast-specific protein 1, platelet-derived growth factor receptor, fibroblast activation protein, and many



**Figure 2** Representative scanning electron and photomicrographs of the three-dimensional arrangement of left ventricular extracellular matrix in the human heart. Samples are from individuals with infiltrative (amyloidosis), non-ischaemic, and ischaemic cardiomyopathy (CM) compared to an unused non-failing donor heart. The top two panels show the matrix in cross-section, with a typical honey-comb structure that is notably less fine and organized, but with distinct patterns, in CM compared to non-CM myocardium. H&E stained sections from the same hearts are shown in the bottom row for comparison. Bars = 40 mm (top row) and 2 mm (middle row). Tissue is courtesy of the Vanderbilt Cardiovascular Institute Biobank and images are shown with permission from Cristi Galindo and Sean Lenihan.

others are unique molecular signatures that allow the identification of cancer and HF abnormal fibroblasts.<sup>72</sup> Given the shared features between cancer and cardiac fibroblasts, anti-neoplastic drugs targeting fibroblasts could be repurposed to treat HF.

## Heart failure driving cancer

An additional mechanistic layer, possibly accounting for the co-occurrence of cancer and HF, is provided by experimental studies indicating that HF itself represents a pro-oncogenic condition. Based on evidence assembled in several reviews, HF is characterized by the activation of neurohormonal systems, including the renin–angiotensin–aldosterone system and the sympathetic nervous system, which are also involved in cancer development and progression.<sup>73,74</sup> Sympathetic nervous system activation induced by physical stressors, such as cold or restraint, may accelerate tumour growth and dissemination in numerous mouse models of malignancy. The modulation of the tumour microenvironment by neurohormonal mediators, like noradrenaline and angiotensin II, seems to play a prominent role in this process.<sup>8,14,73</sup> The systemic sympathetic activation, as seen in HF,<sup>75</sup> affects all the cells of



the body. Studies to unravel the detailed mechanisms by which sympathetic activation promotes carcinogenesis are urgently needed.

## Heart failure aetiologies and incident cancer

A growing body of pre-clinical research indicates that HF-secreted factors mediate or facilitate the development, progression, and dissemination of tumours. In a recent study, failing hearts were shown to induce tumour growth by secreting pro-oncogenic factors into the circulation. The authors performed artery ligation in the hearts of mice genetically prone to develop colorectal cancer. These mice developed eccentric hypertrophy, dilatation, and reduced ejection fraction.

The MI group demonstrated a higher number of intestinal polyps and higher tumour load compared to non-MI mice. The potential effects of haemodynamic load on tumour growth were excluded by transplanting either infarcted or healthy hearts in the cervical region of mice, retaining their native heart *in situ*. The authors postulated that the oncogenic activity of the failing heart was mediated by secreted factors such as SerpinA3, a factor regulating tumour cell survival pathways, and apoptosis.<sup>4</sup> The mechanisms by which these factors exert their function require further validation and future research to uncover heart-specific tumour markers and reveal new therapeutic targets.<sup>76</sup> A recent study indicated that MI accelerates breast cancer growth in mice. The investigators reported increased circulating Ly6Chi monocyte levels and recruitment to tumours in MI mice compared to sham mice. Interestingly, the depletion of these cells abrogated MI-induced tumour growth.<sup>77</sup>

Further validation has been observed in the transverse aortic constriction (TAC) mouse model after implantation of cancer cells. The TAC-operated mice demonstrated bigger tumours, higher proliferation rates, and more metastasis compared to their control. Also, treating cancer cells, *in vitro*, with serum derived from the TAC-operated mice stimulated their proliferation.<sup>78</sup> These results validated the concept of secreted factors in the serum that promote tumour growth.<sup>4,78</sup> The mechanisms by which these factors exert their function require further validation and future research to uncover heart-specific tumour markers and reveal new therapeutic targets.<sup>76</sup>

In the above-mentioned animal studies, two HF aetiologies have been investigated: the MI model is characterized by eccentric hypertrophy and reduced ejection fraction, and the TAC model that develops concentric hypertrophy with preserved ejection fraction. The risk of cancer in human HF with reduced ejection fraction (HFrEF) and HF with preserved ejection fraction (HFpEF), and whether there is a specific interaction between a specific HF subtype and incident cancer, has not been investigated yet.

In the setting of HFpEF, there are many comorbidities such as hypertension, chronic kidney disease, chronic obstructive pulmonary disease, and diabetes. All of these individual comorbidities are known to be associated with incident cancer. Thus, these comorbidities are confounding factors that could affect the association between HFpEF and cancer. No dedicated perspective studies

have been published in which these associations were sufficiently brought to light in the HFpEF setting. Therefore, future studies should account for the comorbidities in multivariable models to assess whether there is a causative effect of HFpEF *per se* on carcinogenesis beyond the cumulative effect of the comorbidities.

## Safety of heart failure treatments and medical radiology

The safety of HF treatments with regard to cancer incidence is still a subject of investigation. Several studies demonstrated a higher lung cancer incidence among patients treated with angiotensin-converting enzyme inhibitors, especially in individuals treated for more than 5 years,<sup>79</sup> and a dose–response relationship between hydrochlorothiazide and both basal and squamous cell carcinoma.<sup>80</sup> But data from a large cohort study could not link cancer prevalence to angiotensin receptor blocker (ARB) treatment, although in subgroup analysis a significant association between ARB and cancers in male genital organs was reported.<sup>81</sup> Large randomized clinical trials with irbesartan, valsartan, and losartan did not show any increase in the overall or site-specific cancer prevalence in patients associated with ARB use.<sup>82</sup> In contrast to the suggestion that HF treatments are possible factors contributing to carcinogenesis, several ongoing clinical trials are investigating the efficacy of CV drugs to prevent cancer or improve outcomes in cancer patients (Table 2).

Moreover, cancer incidence associated with the exposure to medical radiation has been previously evaluated. An observational retrospective cohort detected a correlation between the cumulative dose of CT scan radiation and both leukaemia and brain tumours.<sup>83</sup> Another study reported a cancer risk attributable to radiation exposure from cardiac catheterization.<sup>84</sup> Collectively, these findings suggest that cancer incidence is relatively low, considering the substantial diagnostic and therapeutic value of radiation. However, when considering the annual incidence of CV diseases necessitating examination with CT scans/cardiac catheterization, the overall attributable cancer risk does not lead to a negligible number of cancer cases. It should thus be re-emphasized that careful consideration by the treating physician should be taken before any potentially carcinogenic diagnostic/therapeutic options are considered.

## Cancer driving heart failure

The cardiotoxic effects of anti-cancer treatment leading to a wide spectrum of CV abnormalities including HF have been well established and extensively reviewed. In summary, several cancer therapies cause ventricular dysfunction and cardiomyopathy leading to HF in predisposed individuals.<sup>7</sup> The susceptibility of patients to these toxicities differs markedly, presumably reflecting genetic and epigenetic factors and pre-existing medical conditions. This applies to chemotherapeutic and targeted agents, as exemplified by the anthracycline doxorubicin and trastuzumab. Doxorubicin-related cardiomyopathy involves multiple cellular perturbations including DNA damage,<sup>85</sup> mitochondrial dysfunction,<sup>86,87</sup> activation of cytoplasmic proteases,<sup>88</sup> impaired autophagic flux,<sup>89</sup> and defects in

**Table 2** A selection of ongoing clinical trials investigating the efficacy of cardiovascular drugs to prevent cancer or improve outcomes in cancer patients

Title of the clinical trial	Intervention(s)	Outcome measures	Phase	Identifier
Clinical Research on Treatment of Gastrointestinal Cancer in the Preoperative by Propranolol	Propranolol	Tumour size	I	NCT03245554
Hydrochlorothiazide and Risk of Skin Cancer	Hydrochlorothiazide	Non-melanoma skin cancer	N/A	NCT04334824
Clinical Study of Propranolol Combined With Neoadjuvant Chemotherapy in Gastric Cancer	ACEi	Melanoma skin cancer		
Colorectal Metastasis Prevention International Trial 2	Propranolol	Overall response rate	II	NCT04005365
	Propranolol etodolac	5-year disease-free-survival	II	NCT03919461
	Placebo	Biomarkers in extracted tumour tissue samples assessing pro- and anti-metastatic processes		
		Biomarkers in blood samples assessing pro- and anti-metastatic processes		
		Number of patients with treatment-related adverse events		
		Depression, anxiety, global distress		
		Fatigue		
Efficacy of Chemopreventive Agents on Disease-free and Overall Survival in Patients With Pancreatic Ductal Adenocarcinoma: The CAOS Study	Aspirin	Disease-free survival	N/A	NCT04245644
	Beta-blockers	Overall survival		
	Metformin			
	ACEi			
	Statins			
Propranolol Hydrochloride in Treating Patients With Prostate Cancer Undergoing Surgery	Laboratory biomarker analysis	CREB phosphorylation	II	NCT03152786
	Propranolol Hydrochloride	BAD phosphorylation		
	Questionnaire administration	Distress score		
	Survey administration	Levels of transcripts that reflect ADRB2/PKA activation		
		Plasma catecholamine levels (including epinephrine)		
		Plasma propranolol levels		
		Self-perceived stress		
MELABLOCK: A Clinical Trial on the Efficacy and Safety of Propranolol 80 mg in Melanoma Patients	Propranolol	Effect of propranolol on overall survival for melanoma patients in stage II/IIIA (T2, N0 or N1, M0)	II/III	NCT02962947
	Placebo	Effect of propranolol on disease-free survival for melanoma patients in stage II/IIIA		
		Effect of propranolol on specific mortality for melanoma patients in stage II/IIIA		
		Effect of propranolol on long-term safety in melanoma patients in stage II/IIIA		
Beta Adrenergic Receptor Blockade as a Novel Therapy for Patients With Adenocarcinoma of the Prostate	Carvedilol	Change in biomarkers in prostate biopsy compared to prostatectomy tissues	II	NCT02944201
		Change in serum PSA		
Anti-Cancer Effects of Carvedilol With Standard Treatment in Glioblastoma and Response of Peripheral Glioma Circulating Tumour Cells	Carvedilol	Survival curve of overall survival	I	NCT03980249
		Survival curve of progression-free survival		
		Quantify circulating tumour cells		

**Table 2 (Continued)**

Title of the clinical trial	Intervention(s)	Outcome measures	Phase	Identifier
Use of Propranolol Hydrochloride in the Treatment of Metastatic STS	Propranolol hydrochloride Doxorubicin	Progression-free survival Overall survival	II	NCT03108300
Propranolol Hydrochloride in Treating Patients With Locally Recurrent or Metastatic Solid Tumours That Cannot Be Removed By Surgery	Propranolol hydrochloride	Incidence of toxicity graded according to Common Terminology Criteria for Adverse Events (CTCAE) V. 4.0 Change in vascular endothelial growth factor Effect of beta-adrenergic blockade on the tumour microenvironment Effect of beta-adrenergic blockade on the host immune system Progression-free survival Overall survival	I	NCT02013492

ACEi, angiotensin-converting enzyme inhibitor; N/A, not applicable; PSA, prostate-specific antigen.  
Source: ClinicalTrials.gov.

contractile protein expression<sup>90</sup> and structure.<sup>91</sup> Although the mechanisms are poorly defined, antagonism of HER2 signalling in cardiomyocytes by trastuzumab likely results in both cellular dysfunction and loss of cell survival pathways.<sup>92–94</sup> Immune checkpoint inhibitors, such as ipilimumab, nivolumab, and cemiplimab were developed for multiple tumours. More recently, immune checkpoint inhibitors have been associated with immune-related adverse events and CV complications including pericarditis, vasculitis, and arrhythmias.<sup>95–97</sup>

Besides drugs, chest radiotherapy, mainly for mediastinal lymphoma, carries a risk of restrictive cardiomyopathy that typically develops several years after exposure and may lead to HF.<sup>98,99</sup> Further to the direct toxicity of the aforementioned therapies in the form of cardiomyopathy, other CV complications of cancer therapy, such as myocardial ischaemia, arterial hypertension, pulmonary hypertension, myocarditis or valvular heart disease, also contribute to the development of HF.<sup>100</sup> In addition to established approaches to prevent and/or to treat HF in patients receiving anti-neoplastic therapy (Table 3), there are several ongoing clinical trials investigating the efficacy of CV drugs in patients undergoing potentially cardiotoxic anti-neoplastic treatments (Table 4).

## Heart failure induced by cancer metabolic byproducts

Metabolic alterations in HF affect not only the heart but also several other tissues such as skeletal muscle and liver.<sup>101</sup> Based on pre-clinical studies, it has been postulated that systemic metabolic alterations caused by cancer cells impair cardiac function.<sup>102,103</sup> Potential mechanisms are not limited to alterations in metabolic fuelling of the heart since it is now becoming widely accepted that metabolic intermediates can also act as signalling molecules to alter gene expression, protein function or contribute to epigenetic modifications that ultimately result in ventricular remodelling.<sup>104</sup> Malignancies characterized by somatic mutations in isocitrate dehydrogenase (IDH1/2) gene provide a prominent example of how byproducts of cancer metabolism could alter cardiac function.

**Table 3 Summary of therapeutic recommendations for the management of cancer therapeutic-related cardiac dysfunction**

Anti-neoplastic drug	Cardioprotective drugs/strategies
Anthracyclines	ACEi/ARBs
Daunorubicin	Beta-blockers
Doxorubicin	Statins
Epirubicin	Limit cumulative dose of daunorubicin to <800 mg/m <sup>2</sup>
Mitoxantrone	Limit cumulative dose of doxorubicin to <360 mg/m <sup>2</sup>
Idarubicin	Limit cumulative dose of epirubicin to <720 mg/m <sup>2</sup>
	Limit cumulative dose of mitoxantrone to <160 mg/m <sup>2</sup>
	Limit cumulative dose of idarubicin to <150 mg/m <sup>2</sup>
	Dexrazoxane as an alternative
	Aerobic exercise
Trastuzumab	ACEi/ARBs
	Beta-blockers
All anti-neoplastic drugs	Examine and minimize cardiovascular risk factors
	Treat comorbidities
	Avoid QT prolonging drugs
	Manage electrolyte abnormalities
	Minimize cardiac irradiation

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker.

Adapted from the 2016 ESC guidelines.<sup>98</sup>

Specifically, cancer-associated mutations in IDH1/2 result in a gain-of-function enabling synthesis of 2-hydroxyglutarate (2-HG) from the Krebs cycle intermediate  $\alpha$ -ketoglutarate, and increased circulating levels of 2-HG cause dilated cardiomyopathy by inducing

**Table 4** A selection of ongoing clinical trials investigating the efficacy of cardiovascular drugs in patients receiving potentially cardiotoxic anti-neoplastic treatments

Title of the clinical trial	Intervention(s)	Outcome measures	Phase	Identifier
Evaluation and Management of Cardio Toxicity in Oncologic Patients	ACEi Beta-blockers	Echocardiographic global strain Troponin (ng/mL) ACEi and beta-blocker treatment B-type natriuretic peptide (pg/mL)	N/A	NCT02818517
Cardiotoxicity Prevention in Breast Cancer Patients Treated With Anthracyclines and/or Trastuzumab	Bisoprolol Ramipril Placebo	Left ventricular ejection fraction	III	NCT02236806
S1501 Carvedilol in Preventing Cardiac Toxicity in Patients With Metastatic HER-2-Positive Breast Cancer	Carvedilol Patient observation	Time to the first identification of cardiac dysfunction Incidence of adverse events associated with beta-blocker treatment Rate of first interruption of trastuzumab Rate of death Time to first occurrence of cardiac event Drug adherence	III	NCT03418961
Carvedilol for the Prevention of Anthracycline/Anti-HER2 Therapy Associated Cardiotoxicity Among Women With HER2-Positive Breast Cancer Using Myocardial Strain Imaging for Early Risk Stratification	Carvedilol Placebo	Maximum change in left ventricular ejection fraction Incidence of abnormal left ventricular ejection fraction	II	NCT02177175
Prevention of Anthracycline-induced Cardiotoxicity	Enalapril	The occurrence of cardiac troponin elevation above the threshold in use at the local laboratory, at any time during the study Admissions to hospital for cardiovascular causes Cardiovascular deaths Occurrence of hypo- or hyperkinetic arrhythmias	III	NCT01968200
Risk-Guided Cardioprotection With Carvedilol in Breast Cancer Patients Treated With Doxorubicin and/or Trastuzumab	Carvedilol	Left ventricular ejection fraction Treatment adherence as measured by pill count Adverse events Diastolic function (E/e') by echocardiogram Ventricular–arterial coupling measured by echocardiogram Cardiac strain measurements by echocardiogram Frequency of individuals with clinical heart failure High-sensitivity troponin level N-terminal pro B-type natriuretic peptide level	I	NCT04023110
STOP-CA (Statins TO Prevent the Cardiotoxicity From Anthracyclines)	Atorvastatin Placebo	Left ventricular ejection fraction Number of cardiac events Myocardial fibrosis Troponin T and global longitudinal strain	II	NCT02943590
Statins for the Primary Prevention of Heart Failure in Patients Receiving Anthracycline Pilot Study	Atorvastatin Placebo	Cardiac MRI measured left ventricular ejection fraction within 4 weeks of anthracycline completion	II	NCT03186404
Detection and Prevention of Anthracycline-Related Cardiac Toxicity With Concurrent Simvastatin	Simvastatin Doxorubicin/ cyclophosphamide	Change in echocardiographic global longitudinal strain Number of participants with adverse events as a measure of safety and tolerability Recurrence-free survival with concurrent simvastatin	II	NCT02096588

ACEi, angiotensin-converting enzyme inhibitor; MRI, magnetic resonance imaging; N/A, not applicable.

Source: ClinicalTrials.gov.

mitochondrial damage and myocardial glycogen accumulation via the up-regulation of genes involved in glycogen biosynthesis.<sup>105</sup> Whether similar mechanisms apply to other forms of cancer remains to be explored, but 2-HG accumulation was also observed in response to cancer-induced hypoxia, although the mechanism behind this phenomenon remains unclear.<sup>106,107</sup> Moreover, elevated 2-HG was observed in mouse hearts during ischaemic preconditioning.<sup>108</sup> Further studies are necessary to investigate whether strategies targeting these byproducts can be applied in a clinical setting.

## Cachexia and cardiac wasting in cancer

Cachexia describes a state of involuntary weight loss that is often observed in patients with cancer, particularly in pancreatic, gastro-oesophageal, lung, head and neck and colorectal cancers, reaching a prevalence of 40% to 70% depending on the type of malignancy.<sup>109,110</sup> Weight loss affects all body compartments, but skeletal muscle is particularly prone to be affected early in the course of body wasting. Along with the development of cardiac fibrosis,<sup>111,112</sup> it has been shown in animal models that cancer promotes cardiac atrophy.<sup>113</sup> In all cases, cancer reduced the heart weight in animal models,<sup>114–116</sup> and cardiac function deteriorated in parallel.<sup>117,118</sup> The mechanisms behind cardiac wasting started to be understood, and appear to involve activation of the ubiquitin–proteasome system, autophagy, as well as myocyte apoptosis.<sup>113</sup> Furthermore, tumour necrosis factor, as well as IL-1 $\beta$  and IL-6, seem to be key mediators in this process.<sup>116,119</sup> One study pointed to the direct effects of secreted factors from cancer cells that induce atrophy and metabolic changes in cardiomyocytes, but the exact signalling pathways in cardiomyocytes are still poorly understood.<sup>118</sup> The identified secreted factors were named cachexokines. Cachexokines may be useful as biomarkers for the diagnosis of cancer-induced cardiac complications and might lead to the identification of new therapeutic targets. Furthermore, espidolol, a novel non-selective beta-blocker, demonstrated striking therapeutic and preventive potentials for cancer-related cachexia. Espidolol reversed weight loss, improved and maintained fat-free mass in advanced cachexia in patients with colorectal or non-small cell lung cancer.<sup>120</sup> Animal models suggest that the wasting process affecting the heart is partially attenuated by HF medications and statins.<sup>111,121</sup>

## Translational outlook and steps forward

### Common pathways in heart failure and cancer: a clinical perspective

As discussed above, the bidirectional relationship between the two conditions is promoted by common pathophysiological mechanisms (Figure 3). Besides shared environmental and epigenetic risk factors, and systemic disease interaction, the heightened risk of cancer in HF might partly be accounted for by a simple surveillance bias. Judging from the fact that HF patients need to perform

more hospital visits for their treatment or management, it could be assumed that surveillance bias could be responsible for the higher cancer incidence in this patient group. However, no study has proven this point. On the other hand, the diagnosis of cancer or HF might be rather delayed, partly by attribution of the symptoms of the former to the latter and vice versa.<sup>122</sup> Furthermore, the CV function and predictors of exercise capacity have been shown to be impaired in patients with cancer *per se*, i.e. even before the initiation of cancer therapy.<sup>123</sup> Circulating CV hormones, such as natriuretic peptides, are related to cancer progression and severity, which suggests the presence of subclinical functional and morphological heart damage. This provides hints for HF therapy in cancer patients beyond the focus on the prevention of anti-cancer drug-induced cardiotoxicity.<sup>124</sup>

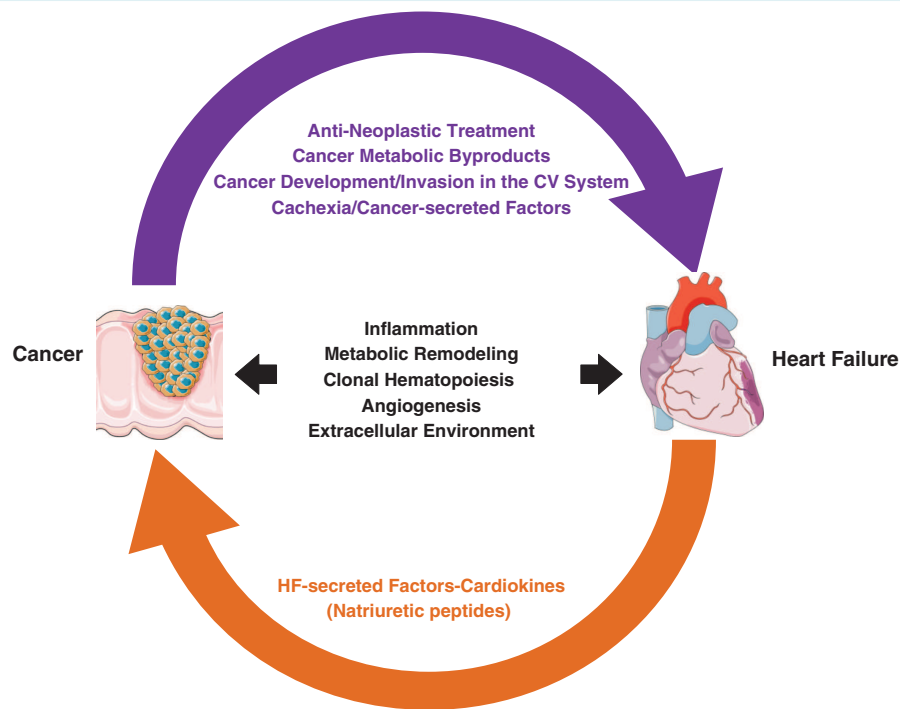
Cancer and HF carry an independent risk of mortality, but also interfere with the optimal treatment of one another, which increases mortality.<sup>122</sup> To overcome these challenges, a close collaboration between cardiologists and oncologists is required and specialists should recognize the benefits of therapy for HF and cancer, and the risks of withholding or sub-optimally treating either or both diseases. The prognostic impact of each condition should always be well defined and considered in the decision-making process.<sup>122</sup> A multidisciplinary approach is encouraged and should include other healthcare professionals, including cardiac rehabilitation, psychology, and palliative care where necessary.

The scientific evidence upon which clinical decisions can be based is very restricted, but epidemiology suggests that the demonstration of cancer in HF patients is an increasingly common problem in an aging population. Recently, the SAFE-HEaRt trial has been designed to test the efficacy of anti-HER2 drugs in patients with mildly reduced cardiac function in the setting of ongoing cardiac treatment.<sup>125</sup> Further, well-designed studies are required to clarify the thresholds at which cancer treatment should not be given to patients with pre-existing HF, and the optimal cardioprotective and surveillance strategies for patients in whom these two worrisome conditions coexist. Modern oncology delivers personalized medicine (e.g. mutation-based) while in cardiology molecular-based personalized medicine is virtually absent. Cardio-oncology should be considered as an opportunity to increase the role of personalized approaches in CV medicine too (e.g. administration of cardio-protective co-treatments).

## The need for appropriate pre-clinical models

Studies in animal and cell systems have been valuable components of translational research in many areas, including the investigation of the biological mechanisms by which cancers interact with the CV system, and vice versa. Coupled with research in disease registries, biorepositories, and clinical trials, findings in cellular and animal models can help to weave together a detailed and mechanistic understanding that paves the way for innovative therapeutic strategies targeting both diseases simultaneously (online supplementary Table S1). Reproducible pre-clinical models with both cancer and HF are required to study the interactions and impact of new therapeutic strategies upon both diseases.





**Figure 3** Graphical presentation that summarizes the proposed common pathways involved in the development and progression of cancer and heart failure (HF). CV, cardiovascular. Illustration elements are from Smart Servier Medical Art.

Review of *in vitro* and pre-clinical work examining the mechanisms of anti-cancer therapy-induced cardiotoxicity over the past 20 or more years demonstrates numerous outcomes.<sup>126–129</sup> These models require further investigation, particularly with regard to understanding the extent to which these findings represent issues faced by humans presenting cancer and heart disease. Also, cell-based assays should be used to test and develop new drugs.

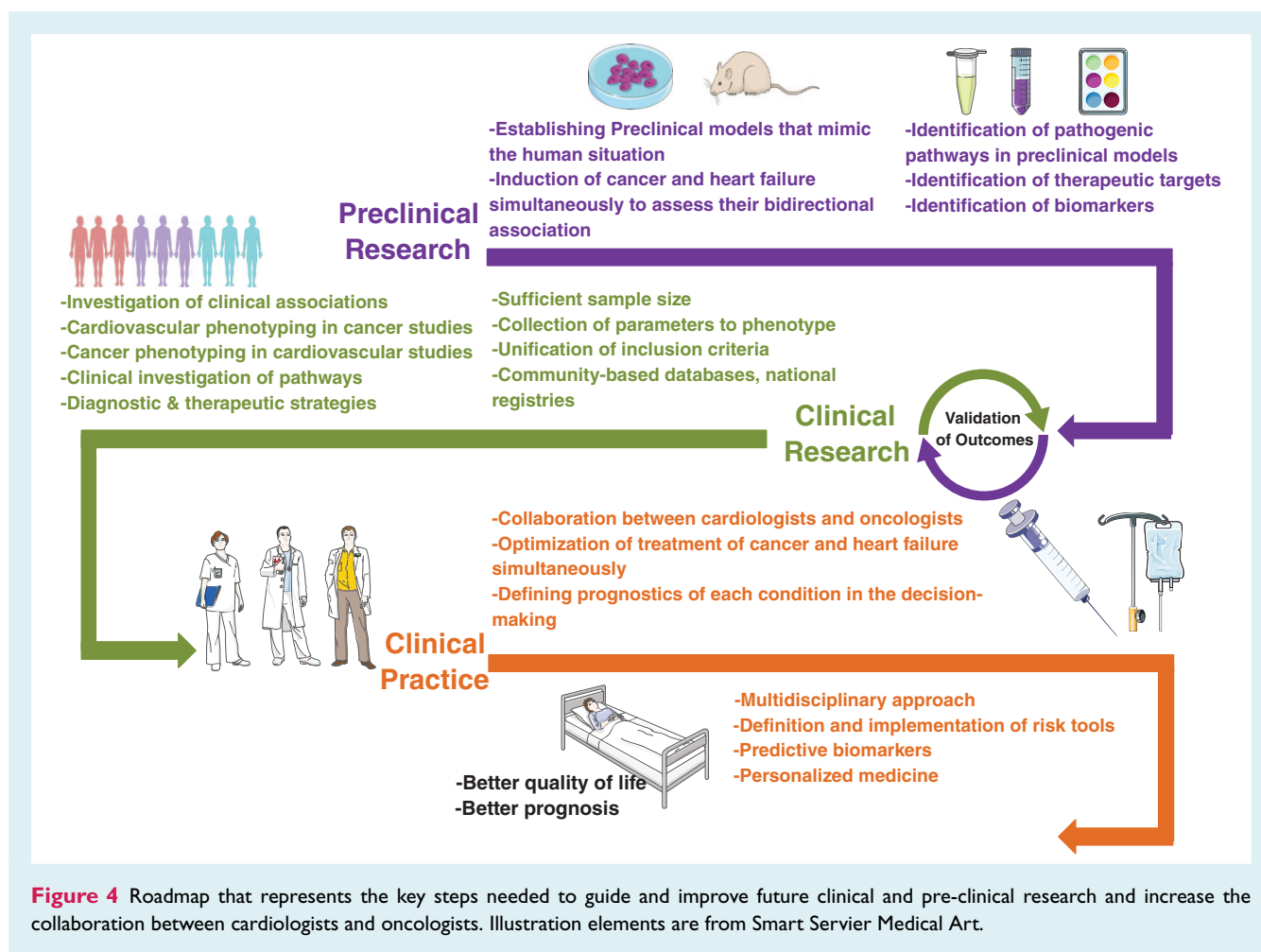
### The need for registries and clinical studies

Specific studies focusing on HF–cancer interactions would be needed to answer important unsolved questions such as defining the characteristics of patients who are more susceptible to present both conditions, identifying some early and specific predictive biomarkers,<sup>130–137</sup> adequately adjusting the management of those patients, and better understanding of shared mechanisms that could lead to target common regulators of HF and cancer. To answer these questions, dedicated registries and studies would need to reach three main requirements.

The first relates to a sufficient sample size to ensure adequate power to detect both conditions. Indeed, the incidence rates of both HF and cancer are strongly related to age, with a steep rise from around 55–60 and the highest incidence rates being in elderly people (80+) (online supplementary Figure S1) showing an overlay of age-specific HF and cancer incidence rates.

However, the connection between cancer and HF is beyond aging. A recent registry-based cohort study investigated the association of congenital heart disease (CHD) with the risk of developing cancer.<sup>138</sup> The authors found that by the age of 41 years, one out of 50 patients with CHD developed cancer. They also reported a twofold higher risk of cancer in children and young adults with CHD compared to healthy matched controls. A long-term follow-up study evaluated cancer incidence in patients with chronic HF from the Danish registries. The cancer incidence rates were higher in all age groups. However, older HF patients ( $\geq 80$  years) had a lower incidence rate than the HF patients of the age group between 70 to 79 years.<sup>11</sup> Also, data from a cohort of peripartum cardiomyopathy patients from Germany and Sweden reported a strikingly higher cancer incidence among (very young) women with peripartum cardiomyopathy compared to age-matched controls (20–50 years).<sup>5</sup> Harmonising national CV and cancer registries is one path to pursue as exemplified by the Virtual Cardio-Oncology Research Initiative (VICORI) in the UK. VICORI created a national linked data resource between the English National Cancer Registration and Analysis Service and the six national CV audits, and will link the datasets using unique identifiers such as NHS numbers to track hospital admission data and mortality for patients in both cancer and CV registries.

Based on these outcomes, systematic screening for cancer should be considered for risk stratification in young predisposed patients, which allows early prevention and optimal management. Similar studies are of pivotal clinical significance as HF and cancer are not limited to a specific age group.



**Figure 4** Roadmap that represents the key steps needed to guide and improve future clinical and pre-clinical research and increase the collaboration between cardiologists and oncologists. Illustration elements are from Smart Servier Medical Art.

Overall, the risk of new cancers is similar or slightly higher than the risk of new HF (with an average of 5–10 per 1000 person per year for both cancer and HF).<sup>139</sup> Consequently, the answers to many unsolved questions in HF–cancer interactions will come from large registries or cohorts of patients (estimated to optimally be >100 000 general comers or >10 000 patients presenting with one or the other condition). However, cancer registries usually report CV mortality, but no cardiac morbidity parameters.<sup>140</sup> Community-based databases, such as health data from the Rochester epidemiological data, have been used to describe a higher risk of new cancer in patients HF<sup>9</sup> or after MI.<sup>10</sup> Similarly, national health insurance registries can offer an appropriate setting to decipher HF–cancer interactions.<sup>11,141</sup>

The second relates to the collection of relevant parameters to better phenotype HF in cancer patients and reciprocally cancer in HF patients.<sup>142</sup> In most clinical studies, both conditions are mutually exclusive, thus hampering specific investigations on HF–cancer interactions.<sup>143</sup> It would also be needed to define a minimal set of markers (such as cardiac biomarkers, electrocardiogram, and many others) that could be simply included in such studies.

The last requirement relates to the constitution of prospective banking of different biological samples (including blood and urine). These samples will notably help in describing pathways

and targets that sustain the common development of HF and cancer.

In conclusion, we now have preliminary insights into factors mediating tumour growth in HF and should not be dismissive of the epidemiological data. Cancer surveillance in the HF population is essential. A holistic rather than a disease-based care plan is essential in HF patients. Future joint research efforts are needed to identify important mediators to strengthen the connection of HF with tumour growth (Figure 4).

## Supplementary Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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